CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PENDIMETHALIN

Chemical Code # 1929, Tolerance # 361
SB-950 # 037

September 22, 1987
Revised 03/31/89, 12/18/89, 9/7/90, 10/28/93, 4/15/97

I. DATA GAP STATUS

Chronic toxicity, rat: No data gap, possible adverse effect

Chronic toxicity, dog: No data gap, no adverse effect

Oncogenicity, rat: No data gap, possible adverse effect

Oncogenicity, mouse: No data gap, no adverse effect

Reproduction, rat: No data gap, no adverse effects indicated at levels below parental toxicity

Teratology, rat: No data gap, no adverse effect

Teratology, rabbit: No data gap, no adverse effect

Gene mutation: No data gap, no adverse effect

Chromosome effects: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotoxicity: Not required at this time

Toxicology one-liners are attached.

All record numbers through 087823 (Document 361-097) were examined. Reconciled with Library printout of 10/15/93 requested by P. Iyer.
In the one-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T970415
Revised by P. Iyer 10/28/93; Gee, 4/15/97.

Record numbers through 147621 (volume 127) have been examined.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED CHRONIC TOXICITY/ONCOGENICITY, RAT

"Additional Studies" below address the thyroid effects in rats.

****361-095 074304** Weltman, R.H., "Chronic dietary toxicity and oncogenicity in rats fed with AC 92,553" (Hazleton Laboratories America, Inc., Study No. 6123-112, 2/13/87). Pendimethalin, AC 92,553, Lot No. AC 3528-129-1, 91.9%, was fed in the diet to Crl:CD(SD)BR rats at 0, 100, 500 or 5000 ppm, 65/sex/group. Of these, 10/sex/group were sacrificed at 12 months. The chief target organ was thyroid, in which increased incidence of follicular cell adenomas was found in both sexes at 5000 ppm (a **possible adverse effect**). At that dose, follicular cell hyperplasia was common, and the majority of rats had atypical pigmented granular material in follicular cells and discolored and/or depleted colloid in the follicles. Also at 5000 ppm, males and females had marked body weight decrements compared to controls, and clinical chemistry findings included elevated cholesterol and elevated gamma-glutamyl transpeptidase levels. **Collectively, these findings suggest that the MTD had been exceeded at the high dose, which was the only dose associated with thyroid tumors or other marked thyroid toxicity**. NOEL = 100 ppm (some follicle cell pigmentation in thyroid: slight body weight decrements in females at 500 ppm). ACCEPTABLE. D. Shimer/ C. Aldous, 9/7/90.

361-097 087823 Reformatted data from 095 074304 (no CDFA review needed).

109 99133, Overview of oncogenic potential. No worksheet.

110 099136, "Effects of Chronic Dietary Administration of AC 92,553 on the Function and Structure of Male Rat Thyroids", (D.E. Bailey, Hazleton Laboratories America, HLA 362-191,

9/10/91). AC 92,553/ Pendimethalin, technical, 92.6%, admixed with the feed at concentrations of 0, 1250, 2500 3750 and 5000 ppm was fed to 125 Sprague-Dawley rats /group for 104 weeks. **Increased incidence of thyroid adenoma, i**ncrease in thyroid stimulating hormone (TSH) levels, along with depressed thyroxine (T4) and free T4 values were observed for the high dose group. Thyroid glands were enlarged and/or darkened and associated with weight increases for the three highest dose groups. The treatment-related changes (non-neoplastic) of the thyroid that were observed include, increases in the incidence of follicular cell pigmentation for the two highest dose groups and follicular cell hypertrophy associated with decreased colloid for the three highest dose groups. Liver changes observed include periportal vacuolization for the two high dose groups and increased incidence of eosino-philic and basophilic foci of cellular alteration, hepatocellular intracytoplasmic eosinophilic inclusions, hepatocellular enlargement and increase in weight for the three high dose groups. Other effects include a reduction in body weight, body weight gains, and food consumption for the three high dose groups. Systemic NOEL = 1250 ppm/day; Oncogenicity NOEL = 3750 ppm/day. Supplemental information. (J. Kishiyama, and P. Iyer, 10/27/93).

009 976069 "A three and twenty-four month oral toxicity and carcinogenicity study of AC 92,553 in rats", (Bio/dynamics, Inc., 8/21/74). [Note that supplementary information in Vols. 61-63 (below) was dated 6/15/81]. Pendimethalin, (grade and purity not characterized) given at 0, 100, 500, and 5000 ppm in diet. **Possible adverse effect:** no NOEL observed (periportal hepatocyte hypertrophy in males at all dosages; hepatocellular cytoplasmic change in both sexes at all dosages). At 500 ppm and above, findings were: cytoplasmic laminated bodies in livers of females, increased secretory granules in thyroid in males, amber to brown urine in both sexes. Increased incidence of uterine endometrial adenocarcinoma in 5000 ppm females. NOT COMPLETE NOR ACCEPTABLE. Various deficiencies noted. Reviews by J. Wong, 3/14/85; and by C. Aldous after receipt of Vols. 61-63, below, 7/24/86.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "invalid".

361-061, 062, and 063 039909-039911 Addenda to study 009:976069, includes microscopic examinations of some tissues which had been preserved in formalin for some years before blocking and staining. Upgrade of study unlikely (see 1-liner, above).

361-124 147603 Copy US EPA RfD/Peer review of pendimethalin, dated 2/12/96 and an earlier document, dated 11/19/92. Also in the volume is an overview of the oncogenic potential by J. Harris, F. Hess and R. Sharma of American Cyanamid, dated 7/27/93.

ADDITIONAL STUDIES

109 099135, "92-Day Thyroid Function Study in Albino Rats with AC 92,553", (J.E. Fischer, Toxicology Department, American Cyanamid Co., Laboratory Report I.D. Study T-0270, 8/5/91). Pendimethalin (AC 92,553, technical) purity 92.6%, was mixed with the feed at concentrations of 0, 100 and 5000 ppm to 80 male Sprague-Dawley rats. Groups of 20 rats/group were sacrificed at days 15, 29, 57 and 92. Food consumption was initially reduced (30%), body weights slightly reduced (approximately 4-7%), and body weight gains reduced for the high dose group. Urine was discolored yellow and yellow-amber for the low and high dose groups, respectively. Incidence of yellow stained fur was increased for the high dose group. Thyroid stimulating hormone (TSH) level was elevated for the high dose group and triiodothyronine (T3) and thyroxine (T4) values were depressed for the high dose and on occasion for the low dose group. Absolute and relative thyroid weights were increased for the high dose group. The incidence of follicular epithelium hypertrophy was increased for the high dose group. Supplemental information. (J. Kishiyama, and P. Iyer, 10/22/93).

361-126 147608 Duplicate of 109 099135.

361-125 147605 "56-day thyroid function study in albino rats with AC92,553." (J. E. Fischer, American Cyanamid, Study L-2366, May 28, 1993)
Male Sprague-Dawley rats were fed 0 (diet), 500 or 5000 ppm pendimethalin for 3, 7, 10, 14, or 28 days. Fifteen per group were sacrificed at each time period. Fifteen per group were allowed 28 days of recovery following 28 days of treatment before sacrifice. Hormone levels

(TSH, T3 and T4) were measured. Morphometric evaluations of thyroid cell height, colloid area and thyroid follicle diameter were included. Most measurements were increased at 5000 ppm by 28 days but recovered to control levels by 28 days post treatment. Electron microscopic evaluation of thyroids from high dose rats showed an accumulation of lysosome-like, electron-dense bodies, with irregular shape, of uncertain origin. Supplemental study. (Gee, 4/14/97)

361-126 147610 "A 14-day intrathyroidal metabolism study in male rats with AC 92,553" (W. J. DeVito and L. E. Braverman, Division of Endocrinology, University of Massachusetts Medical School, Worcester, Mass., Lab. no. UM-91-06-01, 4/16/93) Groups of 10 male Sprague-Dawley rats were fed AC 92,553, 92.98% purity, at 0, 100 or 5000 ppm in the diet for 14 days. Blood from all groups was sampled and serum levels of TSH, T3, reverse T3 and T4 determined. Rats were given ip injections of [131]I (NaI), 25-50 uCi, and sacrificed after 2 hours. Thyroid uptake and metabolism were assessed. No effects were seen at 100 ppm compared with controls. At 5000 ppm, a significant increase in serum TSH and decreases in T3 and T4 were found. No effect on rT3 or thyroid organ weight was reported. There was a significant increase in iodine uptake in the thyroid at the high dose but no difference in the "organification" of iodine or in the percentage of iodine incorporated in MIT, DIT, or T4. Incorporation into T3 was increased at 5000 ppm. The concentration of T4 in thyroid homogenates was similar to controls while that of T3 showed a slight but not significant decrease. Supplemental study. (Gee, 4/17/97)

361-126 147614 "Effect of ingestion of AC 92,553 on biliary excretion and hepatic metabolism of thyroxine" (W. J. DeVito and L. E. Braverman, Division of Endocrinology, University of Massachusetts Medical School, Worcester, Lab. no. UM-92-03-01, 4/16/93) Pendimethalin, 93%, was fed in the diet at 0, 100 or 5000 ppm to male Sprague-Dawley rats, 10 per group, for fourteen days. Blood samples were obtained, allowed to clot, and the serum analyzed for TSH, T3 and T4 concentrations. TSH concentration increased, T3 and T4 decreased at 5000 ppm. No change from control at 100 ppm. Males were injected ip with [125]I-T4 and the liver uptake, biliary excretion and metabolism determined over a 4 hour period. At 5000 ppm, liver weight increased, uptake per liver increased but not on a per gram basis, bile flow

increased, biliary excretion of [125]I-T4 increased with an increased percentage as the T4-glucuronide. Supplemental study. (Gee, 4/18/97)

CHRONIC TOXICITY

RAT

(See combined rat study, above)

DOG

**361-060 039908 "Two-year toxicity study in dogs [AC 92,553]", (Litton Bionetics, December, 1979), Pendimethalin, 91.4%. 0, 12.5, 50, and 200 mg/kg/day by capsule. No adverse effect indicated: NOEL = 12.5 mg/kg/day (based on liver findings, particularly pigmented macrophages, with slightly increased iron deposition). NOAEL = 200 mg/kg/day (see 083:085325, below). A weakness in this study is that a higher dosage range could probably have been tolerated, based on a subchronic study (004:976055). CDFA review of 7/17/86 had indicated not complete, not acceptable: CDFA concerns were (1) dose levels not justified and appeared too low, (2) no ophthalmological exams, (3) no inorganic electrolytes were measured in blood chemistry data, and (4) no tabular summary of clinical observations. Rebuttal submitted 1/12/88 noted negative ophthalmology data in study 004:976055 [90-day FDRL study, 9/12/73: with dosage range to 1000 mg/kg/day], and led to a re-evaluation of the other concerns of the chronic study, considering data from 004:976055. The 3/28/89 CDFA review indicated that the most serious remaining deficiency was lack of adequate dosage justification. Re-review of 9/7/90 considered an addendum (083:085325, below), presenting a second evaluation of liver sections. At the same time, the overall data base on eye toxicity was evaluated. Study is upgraded to ACCEPTABLE status. C. Aldous, 7/17/86, 3/28/89, 9/7/90.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "Core Minimum".

321-083 085325 [addendum to 361-060:039908]. "Histopathology of the liver, an addendum to: Two-year toxicity study in dogs". "Blind" evaluations of previously examined sections of livers from the above LBI study, plus examinations of newly prepared sections by W. Ray Brown, D.V.M, Ph.D., Veterinary Pathologist, at Research Pathology Services, New Britain, PA. Addendum dated 10/19/89. The re-examination confirmed that "pigmented macrophages" were somewhat characteristic of the upper two dosages. The CDFA review considered the liver effects data from the present study, and considered the ophthalmology data base from several chronic and subchronic studies, and concluded that the chronic dog study data requirement is filled. Data suggest a NOEL of 12.5 mg/kg/day (based on limited evidence of liver effects noted above) and a NOAEL of 200 mg/kg/day [based on lack of proper dose-response relationship in record #039908, and on lack of liver findings at 1000 mg/kg/day in subchronic dog study (-004, record #976055)]. Aldous, 9/7/90.

ONCOGENICITY

RAT

(See combined rat, above)

MOUSE

**361-096 074305 Johnson, D. E., "Chronic Dietary Toxicity and Oncogenicity Study with AC 92,553 in Mice", IRDC Report # 141-028, 10/5/88. Pendimethalin, AC 92,553, 92.6%, was administered to CD-1 mice in the diet at 0, 100, 500 or 5000 ppm for 18 months. 55 mice/sex/group were designated for 18-month exposure, and an additional 10/sex/group were allocated for 12-month interim sacrifice. Hematology and ophthalmology were performed, but

not clinical chemistry (hence not a complete "combined" study). No adverse effects. NOEL = 500 ppm (based primarily on slight body weight decrements in high dose females; on slightly increased amyloidosis in several tissues, particularly kidney, in males; and on slight increases in absolute and relative liver/gall bladder weights in both sexes). No oncogenicity was observed. ACCEPTABLE as an oncogenicity study. D. Shimer/ C. Aldous 9/5/90.

361-097 087824 Reformatted pathology tables for 096:074305 per EPA request. No impact on CDFA status, no CDFA written review. Aldous, 8/29/90.

009 019993, 976065 "18-Month Carcinogenicity Study of Herbicide AC 92,553 (Prowl) In Mice"; (Bio/Dynamics, Inc., 72R-747, 4/2/74); Pendimethalin (AC 92,553) Purity and grade not identified. 0, 100, 500, 2500 ppm (high dose raised to 5000 ppm at 8th week), 75 males and 75 females at each dose level and for each of the controls (vehicle control and positive control). Tissues of a maximum of 15/sex/group evaluated microscopically. No adverse effect indicated: Thyroid weights of 5000 ppm males and of 500 and 5000 ppm females were significantly elevated. No microscopic changes in any tissues attributed by investigators to test article. 5000 ppm females had reduced body weight and increased food consumption compared to other groups. UNACCEPTABLE; Not upgradeable. Insufficient information to assess possible adverse effects. (J. Wong, 3/13/85). "One-liner" by C. Aldous, 6/9/87.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "invalid".

REPRODUCTION

RAT

** 103 089055, "Dietary Rat Two-Generation (Two Litters per Generation) Reproduction Toxicity Study", (L.F.H. Irvine and P. Boughton, Toxicol Laboratories Limited, U.K. Report # CBG/2/90, 7/12/90), AC92,553 (pendimethalin), 92.6% purity was fed in the diet (powdered SQC Rat and Mouse No. 3 Breeder diet), for 2 generations with two litters per generation at 0 500, 2500,

and 5000 ppm. Diets were available continuously to the animals from the start of dosing (approximately eight weeks of age) through necropsy of the second generation animals (thirty-two to thirty-four weeks of age). Reduced body weights in the F0 generation at 2500 and 5000 ppm in males (4% to 9%) and females (3% to 16%); in F1 animals at 5000 ppm in males (12% to 15%) and females (14% to 18%), and at 2500 ppm in females (5% to 8%) were observed. Decreased food consumption was reported in F0 and F1 males at 2500 and 5000 ppm. Diminished pup weights for F1a, F1b, and F2a were noted at 2500 and 5000 ppm. No adverse reproductive effects were observed. Parental NOEL = 500 ppm (reduced body weights and food consumption at 2500 and 5000 ppm). Reproductive NOEL = 500 ppm (reduced pup weights at 2500 and 5000 ppm). **Acceptable**. (H. Green, and P. Iyer, 10/17/93).

004 976073 "Three Generation Reproduction Study of AC 92,553 (Prowl) in Rats"; Bio/dynamics, Inc., 72R-74B, 3/6/74; Pendimethalin (AC92,553); Purity and grade not given. Administration in diets of Long-Evans rats to 10 males and 20 females per dose level at 500 and 5000 ppm. Insufficient information to establish NOELs. **No adverse effect indicated (no reproductive toxicity except at dosages which elicit parental effects)**. Findings included slight but consistent reductions in body weight gains of 5000 ppm males and females during growth periods, however food consumption of 5000 ppm animals was at least as high as controls. Fewer pups born in 5000 ppm groups (reason not known). Decreased pup survival and weight gain in 5000 ppm groups, unless dams were taken off treatment during lactation periods. UNACCEPTABLE; Not upgradeable (The chief deficiency is that no adults of any generation were systematically examined microscopically, despite an apparent reproductive effect at the high dose level. Other significant deficiencies included use of only two dose levels, also lack of test article analysis for content, homogeneity, and stability). Insufficient information to evaluate possible adverse effects. (J. Wong, 3/8/85, C. Aldous 10/7/88). (Study re-examined by C. Aldous in rebuttal response of 3/30/89).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "Core Supplementary".

052 016857 Partial duplicate of 004:976073.

TERATOGENICITY

RAT

**042 002911 "Oral Teratology Study in Rats, AC 92,553, Final Report", (Hazleton Laboratories America, Inc., Project # 362-155, 8/17/79). AC 92,553, 94.2% purity, administered by gavage to CD* rats on days 6 through 15 of gestation: 33-34 females/group at 0 (corn oil), 125, 250, and 500 mg/kg/day. Initial review (J. Wong, 3/8/85) classified report as unacceptable, but possibly upgradeable (insufficient information for assessment; lacking justification of dose levels; also lacking individual fetal data to allow independent evaluation by CDFA). The 3/8/85 review noted possible fetotoxicity (delayed ossification, slight). Report was re-reviewed by C. Aldous (9/21/87), who determined that the slight indication of "delayed ossification of extremities" did not warrant flagging as a "possible adverse effect". Report found ACCEPTABLE (3/17/89) following submission of individual fetal data (record 084:064624), and considering chronic and acute toxicity data from other rat studies to justify the dosage range tested. Maternal NOEL > 500 mg/kg/day; Developmental effects NOEL = 250 mg/kg/day (slight increase in ossification delays in extremities). No adverse effects. (H. Green, C. Aldous, 3/17/89).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "Core Supplementary".

084 064624 Individual fetal data for study, 042:002911, above. Data considered in 3/17/89 CDFA review.

003 976070 "Teratogenic Study With AC 92.553 (Prowl) Technical in Albino Rats"; Industrial Bio-Test Labs., Inc (IBT) (Northbrook, IL.), B2324, 12/12/72; UNACCEPTABLE; Not upgradeable; invalid IBT study. (J. Wong, 3/12/85) "One-liner" by C. Aldous, 6/9/87.

RABBIT

**066 039915 "Teratology study in rabbits: AC 92,553 Technical", (Hazleton Laboratories America, Inc., Project # 362-164, 5/11/82). AC 92,553 (Pendimethalin technical), 92.2% purity; administered by gavage on days 6 through 18 of gestation at 0 (corn oil), 15, 30, or 60 mg/kg to 20 artificially inseminated female NZW rabbits/group. Maternal NOEL = 30 mg/kg/day (anorexia, adipsia). No developmental toxicity, hence no adverse effect. Previously reviewed as incomplete ("insufficient information for assessment"): justification was needed for study design, which involved examination of only 1/3 of heads internally; individual fetal data and historical control data were requested (Aldous, 7/25/86 and 9/22/87). Study was re-reviewed after submission of individual fetal data (record 085:064625). Report status is now ACCEPTABLE. (C. Aldous, 3/21/89).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/15/89) notes EPA classification as "Core Minimum".

066 039914 Pilot study for 066:039915, above. Data support choice of dosage groups employed in the primary study. (C. Aldous, 9/22/87)

GENE MUTATION

** 127 147617 Fine, B.C. "Bacterial/Microsome Reverse Mutation (Ames) Test on AC 92,553 (Lot AC 5042-52F) (Purified Sample)". American Cyanamid Company, Genetic Toxicology Laboratory, Study Nos. 5393, 5393A. July 14, 1993. Pendimethalin 99.5%, was initially tested at concentrations of 0 (DMSO), 50, 158, 500, 1581 and 5000 µg/plate, triplicate plates, using Salmonlla typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and a selected locus of Escherichia coli WP2 uvrA in the presence and absence of rat liver metabolic activation (S-9 Mix). A "repeat" assay was performed with pendimethalin concentrations of 0 (DMSO), 500, 750, 1000, 2000, 3000 and 5000 µg/plate using Salmonella typhimurium strains TA98 and TA1538 and Escherichia coli WP2 uvrA^{-} in the presence of metabolic activation. Test article precipitation was observed at 5000 and 1581 µg/plate in the initial assay but was not

mentioned in the repeat assay. Pendimethalin did not increase the number of revertants in either assay. ACCEPTABLE. (Kishiyama and Gee, 4/18/97).

** 127 147618 San, R. H. C. and M. L. Klug. "AC 92,553 Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) and Escherichia coli WP2 uvrA Reverse Mutation Assay with a Confirmatory Assay", (Microbiological Associates, Inc., TC892.501114. May 5, 1993) AC 92,553, purity 90.7%, at concentrations of 25, 50, 100, 250, 500 and 750 µg/plate in triplicate using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and a selected locus of Escherichia coli WP2 uvrA in the presence and absence of rat liver metabolic activation (S-9 Mix) was tested for mutagenicity potential. Test article precipitation occurred at 500 and 750 µg/plate. Pendimethalin did not increase the number of revertants in initial or confirmatory assays. ACCEPTABLE. (Kishiyama and Gee, 4/18/97).

** 126 147616: San, R. H. C. and V. O. Wagner. "AC 92,553 (Lot No. AC 5213-72A): Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) and Escherichia coli WP2 uvrA Reverse Mutation Assay with a Confirmatory Assay", (Microbiological Associates, Inc., TD847.501114. December 3, 1993.) Pendimethalin, purity 92.4%, at concentrations of 25, 50, 100, 250, 500 and 750 µg/plate using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and Escherichia coli WP2 uvrA in the presence and absence of metabolic activation (S-9 Mix) was tested for mutagenicity potential. Test article precipitation observed at 500 and 750 µg/plate. The assay was repeated and Pendimethalin dosages did not induce either base pair substitutions or frameshift mutations. ACCEPTABLE. (Kishiyama and Gee, 4/15/97).

361-127 147619 "CHO/HGPRT mammalian cell forward gene mutation assay on AC 92,553 (Lot No. AC5042-37D)" (L. F. Stankowski, Jr., Pharmakon Research International, Lab. Project PH 314-AC-002-85, 10/24/85; amended report 7/14/93) CHO cultures were treated with pendimethalin (90.9% purity) for 5 hours with Aroclor 1254-induced male rat liver activation at concentrations of 0 (DMSO), 10, 25, 50, 75, 100, 125, 150 or 175 ug/ml, triplicate cultures per concentration for treatment. Without activation, concentrations were 0, 1, 5, 7.5, 10, 20, 30, 40 or 50 ug/ml, 5 hours, triplicate cultures. Following removal of the test material,

cultures were incubated a further 19 hours, then subcultured for approximately 7-day expression period. Relative survival was also determined. Following the expression period, cells were replated for mutation frequency and for cloning efficiency. Positive controls were ethyl methanesulfonate without activation and dimethyl nitrosamine with activation. Both were functional. Treatment with pendimethalin did not induce increased mutation frequency under the conditions of the study. UNACCEPTABLE, not upgradeable (no repeat assay). (Gee, 4/18/1997)

073 51176 "CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay." (Pharmakon International, Inc., Study No. PH 314-AC-002-85, 10/26/85) AC 92,553, 90.9%, lot AC5042-37D; tested at 0, 10, 25, 50, 75, 100, 125, 150, 175 ug/ml with S-9 and 0, 1, 5, 7.5, 10, 20, 30, 40, 50 ug/ml without S-9 (Aroclor induced Rat Liver S-9 activation) uncorrected for purity; 5 hour exposure period (activated and nonactivated); no adverse effect. Test article cytotoxic to CHO cells at 30, 40, 50 ug/ml without S-9, and at 125, 150, 175 ug/ml with S-9. For all other dose levels mutation frequencies per 10^6 survivors were not statistically significantly greater than the negative controls. UNACCEPTABLE (No repeat trial). J. Gee, 6/15/87.

** 067 039916 "Mutagenicity Tests of Typical Prowl Herbicide and of Minor Component CL 94,269" (American Cyanamid, Report submitted to EPA in 1977); Pendimethalin, several lots up to 99% purity; Salmonella strains TA 1535, TA 1537, TA 98, TA 100, E. coli uvrA; Tested at 0, 10, 100 and 1000 ug/plate ± S-9 plate incorporation or 1000 ug/disk; mouse host-mediated at 6.4 and 10.0 mg/mouse; no adverse effect. ACCEPTABLE. JR Gee (7/24/86). NOTE: Previous review of a less complete version of this study (volume 361-052 record number 016859) by J. Wong (3/8/85) resulted in the determination that the study was unacceptable due to insufficient data.

CHROMOSOME EFFECTS

**073 051178 "In Vitro Chromosome Aberration Analysis in Chinese Hamster Ovary (CHO) Cells." (Pharmakon Research International, Inc., Study No. PH320-AC-002-85, 10/29/85); Pendimethalin,

AC 92,553, 90.9%, lot # AC 5042-37D, tested at 0, 10, 50, 100 ug/ml with Aroclor 1254 induced rat liver and at 0, 7.5, 37.5, 75.0 ug/ml without activation. No adverse effect. There were no statistically significant increases in aberrations/cell and proportion of aberrant metaphases at any dose level tested. ACCEPTABLE. J. Gee, 6/15/87.

003 976074 "Dominant Lethal Study In Rats With AC 92,553." (Food and Drug Research Laboratories, Inc., Waverly Division, Lab. Project No. 2006, 10/5/73); Pendimethalin, AC 92,553, Lot No. 1984-79-3; 0, 500 and 2500 ppm administered in feed to 15 male rats/group for 60 days, rats then mated 1:1 with virgin female rats. **Insufficient information to assess possible adverse effects.** UNACCEPTABLE. (Major variances from guidelines, including omission of positive control group, use of only two dose levels, sacrificed females early). (J. Wong, 3/12/85). "One-liner" by C. Aldous, 6/19/87.

052 016858 Partial duplicate of 003:976074.

**109 099134, "Micronucleus Cytogenetic Assay in Mice with AC92553", (D.L. Putman and M.J. Morris, Microbiological Associates, Inc., Laboratory Study No.: T9801.122004, 6/7/91). AC92,553, purity 92.98%, was administered by gavage at concentrations of 0 (corn oil only), 313, 625, or 1250 mg/kg to 15 ICR mice/sex. Bone marrow was sampled at 24, 48 and 72 hours after dosing. There were no statistically significant dose-related increases in the number of micronucleated polychromatic erythrocytes although 6 (4 male; 2 female) mice in the high dose group (1250 mg/kg) died within two days of dosing and had to be substituted with animals from a replacement group. ACCEPTABLE. (J. Kishiyama and P. Iyer, 10/20/93).

DNA DAMAGE

**073 051177 "Rat Hepatocyte Primary Culture/DNA Repair Test." (Pharmakon International, Inc., Study No. PH 311-AC-003-85, 10/25/85); Pendimethalin, AC 92,553, 90.9%, lot AC 5042-37D; treated at 0, 0.003, 0.005, 0.15, 0.3, 0.5, 1.5, 3.0, 5.0, 15, 30, 50, 150, 300, 500, 1500,

3000, 5000 ug/ml, uncorrected for purity; 18-20 hour exposure; no adverse effect. No significant increase in mean net nuclear counts. ACCEPTABLE. J. Gee, 6/15/87.

** 361-127 147621 San, R. H.C. and H.A. Raabe. "AC92,553: Detection of Single Strand Breaks, DNA/DNA and DNA/Protein Cross Links in Rat Testicular DNA by Alkaline Elution." (Microbiological Associates, Inc., Lab Project ID TC724.396, May 5, 1993.) AC 92,553, purity 90.7%, at concentrations of 0 (corn oil), 1250, 2500 or 5000 mg/kg was injected (IP) into 3 adult male Fischer 344 rats/concentration for each time of exposure groups (2, 6 and 24 hours). AC 92,553 under study conditions did not induce DNA single strand breaks in rat testicular DNA nor DNA/DNA & DNA/protein cross links in rat testicular DNA. (Kishiyama and Gee, 4/21/97)

NEUROTOXICITY (Not required at this time.)